New approaches to the assessment and treatment of the idiopathic inflammatory myopathies

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ABSTRACT

The rarity and heterogeneity of the idiopathic inflammatory myopathies (IIM), and the few validated assessment tools available, have limited information to guide the management of patients with polymyositis, dermatomyositis or inclusion body myositis. In light of the need for such tools, the International Myositis Assessment and Clinical Studies Group (IMACS) was formed as a multidisciplinary consortium of rheumatologists, neurologists, dermatologists, physiatrists and other myositis experts to develop consensus and standards for the conduct and reporting of myositis studies, and to facilitate myositis research. IMACS has developed consensus core set measures of disease activity, disease damage and patient-reported outcomes, and compiled a preliminary definition of improvement. The IMACS tools assist in the evaluation of the extent of disease activity and damage, although other approaches—including key clinical features, laboratory tests, muscle T1 and short τ inversion recovery MRI and immunological markers—are also helpful. Clinical remission is a realistic objective for most patients and should be pursued aggressively to optimise outcomes. Physical therapy and rehabilitation should be applied early and consistently to achieve optimal strength and function. Treatments that have been developed for other immune-mediated diseases are also being used and tested in the IIM, and some have shown anecdotal evidence of benefit. Recent advances in understanding the pathogenesis of myositis, development of assessments and treatments for other diseases that can be applied to myositis, and international collaborations and consensus standards for evaluating the IIM, all promise improvements in the assessment and treatment of myositis in the future.

The idiopathic inflammatory myopathies (IIM), also called myositis syndromes, are systemic autoimmune diseases defined by chronic muscle inflammation of unknown cause.[1] The most common clinical forms are polymyositis, dermatomyositis and inclusion body myositis (IBM); however, other clinically useful phenotypes with different risk factors and prognoses are also defined by clinical features and pathology as well as certain autoantibodies seen mainly in patients with myositis (table 1).[2] Although the IIM are rare, they are the most commonly acquired chronic muscle diseases in adults, with an estimated prevalence of 10–20 per 100 000. Their aetiology remains unknown but these diseases probably result from chronic inflammation induced by a combination of the necessary and sufficient genetic and environmental risk factors.[3 4]

The myositis syndromes are diagnoses of exclusion. The many infections, metabolic myopathies, dystrophies and other conditions that resemble these disorders should first be considered and then ruled out by careful history taking, including medical, family and exposure histories, by physical examination and by directed laboratory testing.[1] Treatment is directed at suppressing inflammation with therapeutic agents and muscle strengthening exercise; however, the specific approaches to use for an individual patient are based mainly on anecdote and custom rather than controlled trials.[5] Part of the difficulty in interpreting the few IIM therapeutic studies that are available is the lack of common diagnostic approaches, trial inclusion and assessment criteria and definitions of improvement.[6]

GROUPS DEVELOPING CONSENSUS APPROACHES TO THE CONDUCT AND REPORTING OF MYOSITIS CLINICAL TRIALS

To examine the lack of consensus about the many aspects of clinical studies in myositis, several international consortia have been organised, including the International Myositis Assessment and Clinical Studies Group (IMACS) and the Paediatric Rheumatology INternational Trials Organisation (PRINTO). Established in 2000 by Lisa Rider, Frederick Miller and David Isenberg, IMACS is a multidisciplinary consortium of over 150 adult and paediatric rheumatologists, neurologists, dermatologists, physiatrists, physical therapists, nurses, statisticians and other myositis experts. Its objectives are to develop consensus and standards for the conduct and reporting of studies in adult and juvenile myositis and to facilitate collaborative myositis research. All those with an interest in myositis are encouraged to join IMACS (http://www.niehs.nih.gov/research/resources/collab/imacs/main.cfm). The IMACS website contains study announcements, provides validated outcome measures and training materials and publications, with additional information available to members, including meeting presentations and member lists.

PRINTO is an international research network founded by Alberto Martini and Nicolino Ruperto in 1996 that focuses specifically on paediatric myositis clinical trials. PRINTO includes more than 350 centres worldwide, with a goal to foster, facilitate and coordinate the development, conduct, analysis and reporting of multicentred, international clinical trials and/or outcome standardisation studies in children with paediatric rheumatic diseases (http://www.printo.it/).

DEVELOPMENT OF PRELIMINARY CORE SET MEASURES AND DEFINITIONS OF IMPROVEMENT

Both IMACS and PRINTO have developed preliminary core set measures for the assessment of disease activity in myositis, with the PRINTO measures for juvenile dermatomyositis only (table 2). IMACS and PRINTO have also developed preliminary core sets for damage and patient-reported outcomes.[7 8] These core sets have undergone some validation testing and are considered partially validated at this time.[8–10] Many of the core set measures are being used in ongoing natural history studies and clinical trials, and although they were developed primarily for use in clinical trials, some doctors are using these tools in clinical practice.

Table 1 Myositis phenotype classifications*

Clinicopathological phenotypes
Polymyositis
Dermatomyositis
Inclusion body myositis
Myositis with another connective tissue disease
Cancer-associated myositis
Necrotising myositis
Eosinophilic myositis
Granulomatous myositis
Focal/nodular myositis
Macrophagic myofasciitis
Ocular/Orbital myositis
Serological phenotypes
More myositis-specific
Anti-Jo-1
Anti-Mi-2
Anti-SRP
Anti-p155 (TIF-1 γ)
Anti-MJ (NXP-2)
Less myositis-specific/unknown
Non-Jo-1 anti-synthetases
Anti-PM/Scl
Anti-Ku
Anti-U1-5 RNP
Anti-CADM-140 (MDA-5)
Anti-200/100-kd (HMGCR)

*Modified from Miller.[15] HMGCR, 3-hydroxy-3-methyl-glutaryl-CoA reductase; MDA-5, melanoma differentiation associated antigen 5; RNP, ribonucleoprotein; SRP, signal recognition particle; TIF, transcriptional intermediary factor.

Definitions of improvement have also been developed through data-driven methods combined with consensus conferences (table 3).[11 12] One of the most used definitions is similar to the American College of Rheumatology 20,[13] and requires at least a 20% improvement in three or more core set measures with worsening of no more than two measures by at least 25%, which cannot be manual muscle strength testing. Nonetheless, other consensus preliminary definitions of improvement have also been developed and are in use in studies today. These definitions need prospective validation in additional randomised controlled trials. Initial experience with these definitions suggests possible areas for improvement in increasing sensitivity and specificity, and better discriminant validity. Efforts are underway to reassess these definitions, and to develop measures that assess greater levels of improvement beyond the minimal clinically important one.

DEVELOPING CONSENSUS ON CLINICAL TRIAL DESIGNS

IMACS has also conducted Delphi surveys and held a conference to develop consensus on clinical trial design.[6] Currently, consensus has been achieved for inclusion and exclusion criteria for trial entry, clinical subgroups to be included in trials, allowable concomitant treatment, duration of placebo use, trial duration, assessment intervals during treatment, safety assessments, core set measures to be collected and definitions of improvement to be included as trial end points, preliminary criteria for worsening, definitions of complete clinical response and remission and post hoc stratifications.

DISTINGUISHING BETWEEN DISEASE ACTIVITY AND DAMAGE

A critical part of the evaluation of a patient with myositis is to determine in all affected organ systems the degree of continuing inflammation contributing to disease activity that might respond to immunosuppressive treatments, and the degree of fibrosis or scarring resulting in disease damage that will not respond to those treatments. Although many different approaches have been helpful, this is a difficult task in some subjects who have longstanding disease.[5] These approaches include directed physical examination, laboratory testing, T1 and short τ inversion recovery (STIR) MRI of the thighs,

Table 2 Proposed International Myositis Assessment and Clinical Studies Group (IMACS) and Paediatric Rheumatology INternational Trials Organization (PRINTO) preliminary core set measures for disease activity assessment in adult and juvenile idiopathic inflammatory myopathies*

Domain	Core set measure
Global activity	Physician global disease activity assessment by Likert or visual analogue scale
	Parent/patient global disease activity assessment by Likert or visual analogue scale
Muscle strength	MMT by a 0–10 point or expanded 0–5 point scale to include proximal, distal and axial muscles.+ (the CMAS been chosen by PRINTO as an alternative measure)
Physical function**	Validated patient/parent questionnaire of activities of daily living—HAQ/CHAQ Validated observational tool of function, strength and endurance—CMAS
Laboratory assessment	At least two serum muscle enzyme activities from the following: CK, aldolase, LD, AST, or ALT (not included in the PRINTO core set)
Extraskeletal muscle disease	The MDAAT or another validated approach that is comprehensive and assesses cutaneous, gastrointestinal, joint, cardiac and pulmonary activity
Global tool	(the DAS and MDAAT are in the PRINTO core set for this domain)
Health-related QoL	(the CHQ and PhS are in the PRINTO core set)

*Modified from Rider[39]; PRINTO definitions when different from IMACS definitions are in parentheses.
ALT, serum activity of alanine aminotransferase; AST, serum activity of aspartate aminotransferase; CHAQ, childhood HAQ; CMAS, Childhood Myositis Assessment Scale; CK, serum activity of creatine kinase; CHQ, Childhood Health Questionnaire; DAS, Disease Activity Scale; HAQ, Health Assessment Questionnaire; LD, serum activity of lactate dehydrogenase; MMT, manual muscle testing; MDAAT, myositis disease activity assessment tool; PhS, Physical Summary Score.
+Not recommended for children less than 4 years of age; **One validated tool is recommended for adults and children more than 4 years of age and two tools for children less than 4 years of age.

Table 3 The IMACS and PRINTO preliminary definitions of improvement using the core set measures*

IMACS		
Adult Myositis	**Paediatric Myositis**	**PRINTO – Paediatric Myositis**
A1 Three of any six improved ≥20%, no more than two worse by ≥25%, which cannot be MMT	P1 Three of any six improved ≥20%, no more than two worse by ≥25%, which cannot be MMT	Three of any six improved by ≥20%, no more than one worsened by >30%, which cannot be muscle strength
A2 MD global improved >30% and MMT improved 1%–15%, OR MMT improved >15% and physician global improved >10%, no more than two worse by ≥25%	P2 Three of any six improved ≥20%, no more than two worse by ≥25%	Three of any six improved by ≥20%, no more than two worsened by ≥25%, which cannot be muscle strength (IMACS definition P1)
A3a MMT improved by at least 15% or MD global activity improved by >30% and MMT improved by 1%–15% and no more than two worse by ≥25%	P3 Three of any six improved ≥20%	Three of any six improved by ≥20%, no more than two worsened by >30%, which cannot be muscle strength
A3b Three of any six measures improved by ≥20%, with no more than two worse by ≥25% A5a MD global activity improved by >30% and MMT improved by 1%–15% or MMT improved by >15% and MD global activity improved by >10%	P4 MD global improved >30% and MMT improved 1%–15%, OR MMT improved >15% and physician global improved >10%, no more than two worse by ≥25%	Two of any six improved by ≥40%, no more than one worsened by >30%, which cannot be muscle strength
A5b Three of any six measures improved by ≥15%, with not more than one worse by ≥25% (which cannot be MMT)	P5 Three of any six improved ≥15%, no more than one worse by ≥25%, which cannot be MMT	Two of any six improved by ≥30%, no more than one worsened by >30%, which cannot be muscle strength

*Modified from Rider *et al*.[11] and Ruperto *et al*.[12] Abbreviations per table 2.

repeated muscle biopsies and the use of IMACS tools. For example, the T1 MRI is helpful in assessing muscle anatomy for loss of volume and fatty replacement that are indicators of damage, while the STIR MRI assesses water content of tissues that relates to inflammation and disease activity in diagnosed myositis. Laboratory measures that appear to correlate well with active disease include flow cytometry evaluation of certain circulating cellular phenotypes, neopterin and factor VIII-related antigen levels, myositis autoantibody levels and type I interferon signatures.[14]

MANAGEMENT OF MYOSITIS

No agents have been approved by the Food and Drug Administration for use in patients with myositis, and treatment remains challenging even for those with extensive experience in managing patients with IIM. The goals of myositis management are to ensure an accurate diagnosis and reassess patients with refractory disease for other causes of myopathy; identify all relevant manifestations of disease; identify and minimise all risk factors for poor prognosis; define the extent of disease activity and disease damage in all affected systems; and develop an individualised treatment plan to achieve remission, taking into account expectations, manifestations, prognosis and risk factors for adverse events to treatments. Because different myositis phenotypes (table 1) have varied clinical presentations, responses to treatment and prognoses, all those factors need to be carefully determined and considered before choosing treatments.[15] The primary treatments for myositis include corticosteroids and other immunosuppressive agents, which decrease the inflammation that contributes to disease activity, and physical therapy to rebuild muscle strength and function.

Methotrexate and azathioprine are the most commonly used corticosteroid-sparing agents.[5] Based on open-label trials and case series, however, hydroxychloroquine,[16] mycophenolate,[17 18] ciclosporin or tacrolimus treatment,[19 20] cyclophosphamide,[19 21] and intravenous gammaglobulin,[22–24] benefit some patients who do not respond to methotrexate or azathioprine. Biological agents approved for use in other rheumatic diseases are also promising. Experience with anti-tumour necrosis factor agents has been mixed, with some evidence of efficacy but some indication that they may actually worsen or induce myositis.[25–29] Rituximab has shown more evidence of efficacy, even in phenotypes with poor prognoses.[30–32]

Few studies have assessed combination immunosuppressive treatment in myositis. An open-label trial suggested that combination methotrexate and azathioprine may benefit patients who had not responded adequately to either agent alone.[33] Given the complementary modes of action of many agents, and preliminary evidence of efficacy of combination treatment in other autoimmune diseases, this should be a promising area of research in the future.

No controlled studies support aggressive early treatment in patients with poor prognosis; however, anecdotal evidence in patients with poor prognostic features suggests that adding additional immunosuppressive treatment to corticosteroids early in the disease course may improve outcomes.[19 34 35]

The treatment of IBM has been controversial and unsatisfactory.[19] Although some investigators do not believe that immunosuppressive treatment is helpful in IBM, anecdotal reports and retrospective reviews of corticosteroid and cytotoxic treatment, a prospective open-label trial of intravenous gammaglobulin, and a randomised trial of combination oral methotrexate plus azathioprine versus high-dose methotrexate with leucovorin rescue,[36] all provide limited evidence that the rate of functional deterioration can be decreased or stabilised and strength can be improved in a subset of patients with IBM.[37] Physical therapy and exercise, however, clearly play the most important role in long-term IBM care.

FUTURE DIRECTIONS

Adequately powered multicentre trials using validated outcome measures are needed to define the best treatment options for the IIM and the major myositis phenotypes. An approach similar to that used in many cancers and other systemic rheumatic diseases might be envisioned for myositis, which would include an aggressive remission-inducing phase followed by a maintenance phase of treatment with the goal being to return patients as much as possible to their predisease state and without evidence of disease activity.[5] The recent advances in new treatments for other diseases,[38] and new international collaborations and standards for outcome assessments, all promise the hope of developing new treatments for myositis and improving the outcome of patients with myositis.

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